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Research report

Retrograde amnesia after electroconvulsive therapy: A temporary effect?

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A B S T R A C T

Objective: Although electroconvulsive therapy (ECT) is generally considered effective against depression, it remains controversial because of its association with retrograde memory loss. Here, we assessed memory after ECT in circumstances most likely to yield strong retrograde amnesia.
Method: A cohort of patients undergoing ECT for major depression was tested before and after ECT, and again at 3-months follow-up. Included were 21 patients scheduled to undergo bilateral ECT for severe major depression and 135 controls matched for gender, age, education, and media consumption. Two memory tests were used: a verbal learning test to assess anterograde memory function, and a remote memory test that assessed memory for news during the course of one year.
Results: Before ECT the patients' scores were lower than those of controls. They were lower again after treatment, suggesting retrograde amnesia. At follow-up, however, memory for events before treatment had returned to the pre-ECT level. Memory for events in the months after treatment was as good as that of controls.
Limitations: The sample size in this study was not large. Moreover, memory impairment did not correlate with level of depression, which may be due to restriction of range.
Conclusions: Our results are consistent with the possibility that ECT as currently practiced does not cause significant lasting retrograde amnesia, but that amnesia is mostly temporary and related to the period of impairment immediately following ECT.

1. Introduction

Electroconvulsive therapy (ECT) is generally considered to be an effective treatment for severe depression (Sackeim et al., 1993, 2000, 2009; Reisner, 2003), but that has not stopped it from being controversial. Most criticism, from outsiders and from patients that have undergone ECT, centers on the purported loss of memory (Rose et al., 2003). ECT is reported to cause anterograde amnesia (an inability to form new memories), but this is usually restricted to the period immediately following the ECT. On the other hand, retrograde amnesia (loss of remote memories) has been argued to be both significant and permanent (reviewed in Fink, 2001).

Earlier studies have documented large memory deficits after a course of ECT. For example, in a seminal study, Squire et al. (1976) found that memories from the last 6 years were severely affected by a course of ECT. In the last decades, however, new techniques (such as the switch from sinusoidal to brief pulse current) have resulted in fewer cognitive side-effects. Anterograde amnesia, which in the 1970s could be as severe as that of dense amnesics (Cohen and Squire, 1981), has recently been shown to be relatively mild (Brodaty et al., 2001; Sackeim et al., 2009). Moreover, it tends to be restricted to a period of confusion immediately following ECT. Studies that include a follow-up of 2–3 months after treatment report

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better memory at follow-up than immediately after ECT or even before the treatment (Sackeim et al., 1993). These improvements over and above the pretreatment level are correlated with the lifting of depression (Brodaty et al., 2001).

However, retrograde amnesia is still reported after ECT, even in more recent studies. It is often severe for memories laid down directly prior to treatment (O'Connor et al., 2008) while remote memories are to some extent spared (Lisanby et al., 2000). In some cases the amnesia partially lifts during the months of recovery (Lisanby et al., 2000; Sackeim et al., 2000, 2007) whereas in others it does not (Sackeim et al., 1993). At follow-up years after ECT, some retrograde amnesia relative to matched controls is still found (Kho et al., 2006). Retrograde amnesia is particularly marked for bilateral, as opposed to unilateral, electrode placement (Sackeim et al., 1993, 2000, 2007, 2009).

However, the actual extent of retrograde amnesia is not yet established. After the seminal work of Squire and colleagues (Squire et al., 1976; Cohen and Squire, 1981) ECT research has rarely focused on retrograde amnesia. Therefore, few studies have, for example, included a control group. Moreover, many studies have relied on autobiographical memory tests (Sackeim et al., 1993, 2000, 2009) which are known to be sensitive to confabulation (Meeter et al., 2006), do not allow memories to be precisely dated and, since such tests tend to rely on free recall by the participant, are very sensitive to the recall deficits typically found in depression (Taconnat et al., 2010).

The present study therefore tests remote memory after ECT using a design that is maximally sensitive to lasting retrograde amnesia. This included testing patients on three occasions, compared with a matched non-depressed control group. Moreover, an objective questionnaire was used with questions focusing on memories previously shown to be most sensitive to ECT, i.e. those from up to one year prior to ECT (Squire et al., 1976; Cohen and Squire, 1981).

2. Method

2.1. Participants

A total of 21 patients at the Erasmus Medical Center (EMC) participated in the study, which was approved by the medical ethical committee of the EMC. Each subject was diagnosed with depression according to the DSM-IV criteria using the SADS (Schedule for Affective disorders and Schizophrenia, Endicott and Spitzer, 1978). Nineteen of 21 patients suffered from major depression with melancholic features; in four of these the depression also had psychotic features. From patients deemed competent to consent by their treating psychiatrist, written informed consent was obtained after providing a complete description of the study. For those whose competence to consent was in doubt, written consent was obtained (after providing a complete description of the study) from the patient and from the family or legal guardian (s). All patients were observed during a medication-free period of 5 days before treatment started.

Grounds for exclusion were alcohol or drug dependence, a diagnosis of dementia or other neurological conditions, endocrinologic conditions and, for participants aged 65 years or older, a Mini-Mental State Examination (MMSE, Folstein et al., 1975) score of 24 or lower.

A sample of 131 adults from the general population was used as a control group. The control group was matched with the patient group for gender, age, level of education and the number of newspapers read over the course of one week (as estimated by the participants). The controls were recruited via an unrelated study on epilepsy, but did not themselves suffer from epilepsy.

2.2. Design

Patients were tested on three occasions: the day before the start of treatment, within 3 days after treatment had ended, and 3 months after treatment. These three occasions are referred to as pre-ECT, post-ECT and Follow-up. On each occasion, patients were administered the 10-Word Test (10-WT) for anterograde memory function, and the Daily News Memory Test-ra (DNMT-ra) for retrograde memory. Both tests were administered via a computer. Moreover, the two research psychiatrists rated the participants' state with the Hamilton Depression Rating Scale (HDRS, Hamilton, 1960). During the trial, interrater sessions with the investigating psychiatrists took place once every month (from these sessions an interrater reliability of $\kappa = 0.95$ was computed). The MMSE (Folstein et al., 1975) was administered before treatment only, and only to the four participants older than 65.

ECT was administered twice weekly and applied bilaterally with a brief pulse, constant current apparatus (Thymatron System IV, Somatics, IL, USA). Seizure threshold, defined as the stimulus dosage that elicited a seizure of at least 25 s according to the cuff method, was determined during the first session with empirical stimulus titration. If the starting stimulus dose failed to elicit a seizure of at least 25 s, stimulus charge was increased according to the titration schedule and the patient was restimulated after 30 s. For the second treatment, the stimulus dosage was set at 1.5 times the initial seizure threshold.

During the course of ECT, stimulus dosage settings were adjusted upward to maintain seizure duration of at least 25 s as measured with the cuff method. Anesthesia was achieved during the ECT sessions with intravenous administration of metoclopramide 10 mg, glycopyrrolate 0.002–0.003 mg/kg, a bolus injection of alfentanil 0.010–0.015 mg/kg and 0.2–0.3 mg/kg propofol followed by succinylcholine 0.5–1.0 mg/kg for muscle relaxation. Patients were withdrawn from all psychotropic medication at least 5 days before ECT and were maintained drug-free during the course of ECT.

Each week patients were rated with the HDRS. Treatment ended when a score below 7 had been reached, or when improvement had plateaued for 4 sessions in a row, or when no improvement was observed during the course of 10 sessions.

2.3. Measurements

The Ten-Word Test (10-WT), used as a measure of anterograde memory function, is a verbal learning test in which 10 concrete nouns are studied for 2 s each. Study is followed by a thirty-second interval of counting backwards from a three-digit number in threes to ensure that no items are active in working memory; then, words have to be free-recalled (Spaan, 2003). The score consists of the total number of words recalled on three study-test trials (range 0–30).

Retrograde memory was measured with the Daily News Memory Test-ra (DNMT-ra, Meeter, 2003), in which participants answered questions about news events from the past year. Each question was first presented in recall format: participants saw the question and an empty box, and could type an answer; these were scored automatically. When a participant did not answer a question correctly they were shown four possible answers in random order and were required to select one (i.e., a recognition format). The test consisted of forty questions. Each of four consecutive three-month periods (i.e., the whole test covered the whole the past year) was covered by ten questions.

The test and individual questions were created through a script. Events that were dateable and that received front-page attention in a major Dutch newspaper were deemed suitable for questions. A headline about this topic was then transformed into a question by taking one of the roles out and replacing it by an interrogative clause. This guaranteed that each question had a simple, determinate and unambiguous answer. Care was taken not to formulate questions in such a way that later news would include the answer (e.g., not "Who won the 2008 US presidential elections", because its answer is contained in every news bulletin about Barack Obama). For a recognition version, three lures were created by freely associating on either the answer or other parts of the headline. These questions were then placed on a public website (www.memory.uva.nl/testpanel), where about 100 volunteers a week answered random samples of questions as part of a news test (for an analysis of volunteer data, see Meeter et al., 2005). Sample questions are given in Table 1.

Every two weeks, a script would automatically generate a DNMT-ra from the data gathered from the volunteers. First, a mathematical model (Murre et al., 2007) was used to extract for each question an acquisition parameter that indexed the likelihood of successfully storing the underlying news item. This parameter was derived by deconvolving item difficulty from the volunteer characteristics and the effects of forgetting (Meeter, 2003). The acquisition parameters were then used to select 10 questions from each of the consecutive three-month periods. Questions were selected in such way that each period had an equal average difficulty. This means that the questions should be equally easy to answer at the moment that the news event took place (i.e., retention interval 0). For a normal participant, the combined effect of equal difficultly and forgetting would result in a standard forgetting curve.

Patients and controls were recruited from 2003 up to 2009. During that period, a new DNMT-ra was created biweekly, and participants always received the most recent one. For each test, items were selected from a large pool. Patients, who were tested three times on the DNMT-ra, thus received new tests with little overlap in questions from one testing occasion to the next.

2.4. Data analysis

Patient and control demographics were compared using a Chi-square test for categorical and t-tests for continuous variables, both two-sided. To determine whether patients differed from controls on the pre-ECT test occasion, an ANCOVA on DNMT-ra scores was performed with group as between-subject variable, period tested as within-subject variable, and gender, age, education and newspaper consumption as covariates.

We then investigated whether ECT had caused retrograde amnesia by comparing DNMT-ra scores for the pre- and post-ECT test occasions with an ANCOVA, with test occasion and period as within-subject variable, and with gender, age, education and newspaper consumption as covariates (all analyses were repeated without covariates; the results were similar and will not be reported, with one exception where the analysis without covariates pointed to a different conclusion than the one with). The most recent period was left out of this analysis to avoid contamination by anterograde amnesia (i.e., by the effect of ECT on learning during the ECT period). To test for lasting retrograde amnesia, we compared the pre-ECT test occasion with the follow-up test occasion in an ANCOVA with the same factors. This time the two most recent periods were left out to avoid contamination by the effects of ECT on learning.

To investigate any lasting effect of ECT on learning, performance on the most recent period during follow-up was compared with the performance of controls for the same period, with an independent-samples *t*-test. All these

Table 1
Sample questions from the DNMT-ra, with for each question the date on which it was created, the correct answer, a sample alternative answer (one of three) and an example of a string whose match with the response of the participant would have led the response to be scored as correct (e.g., any response containing the string "theft" would have been scored as correct for the first question).

Date	Question	Correct answer	Example alternative	Example match
08 July 2005	What was the name of the popular video game that had to be re-rated on July 8, 2005 because it had hidden graphic sexual content?	Grand Theft Auto: San Andreas	Need For Speed: Underground	Theft
29 March 2006	What was the name of the former president of Liberia, who was arrested in Nigeria on March 29, 2006?	Charles Taylor	John Brown	Charles
29 July 2007	Which cyclist won the Tour de France on July 29, 2007?	Alberto Contador	Cadel Evans	Albert
24 Jan. 2008	Which French bank announced on January 24, 2008 that it had uncovered a $7 billion fraud?	Societe Generale	Credit Agricole	Soci
26 Nov. 2008	Which Indian city was struck by several coordinated terrorist attacks on November 26, 2008 resulting in more than 100 deaths?	Mumbai	New Delhi	Mum

analyses on DNMT-ra scores were done separately for recall and recognition.

Anterograde amnesia was investigated with an ANCOVA on the 10-WT data with test occasion as within-subject variable, and with gender, age, education and newspaper consumption as covariates. The relation between anterograde and retrograde amnesia was investigated using correlations.

3. Results

3.1. Group characteristics

Table 2 lists the demographic characteristics of the patients and controls. Patients did not differ from controls for age, $t(150)=1.18$, $p=0.24$; gender, $\chi^2=0.01$, $p=0.975$, education, $t(150)=0$, $p=0.5$, or newspaper consumption, $t(150)=0.569$, $p=0.570$.

3.2. Level of depression

All patients (except one) improved sufficiently over the course of 10 weeks to finish treatment and be considered in remission (the remaining patient was in remission at follow-up). Average HDRS scores decreased between the pre-ECT and post-ECT test occasions, $t(20)=8.68$, $p<0.001$ (Table 3) and then remained mainly stable until the follow-up test occasion, $t<1$. On average, the period between the first and the last ECT session was 54 days (SD 17.8; range 27–102), with the mean number of ECT sessions equal to 12.3 (SD = 4.2, range 6–19). Neither measure correlated significantly with either post-ECT HDRS scores or memory impairment after ECT ($p>.355$ for all correlations).

3.3. Retrograde amnesia

Fig. 1 and Table 4 show the performance on the DNMT-ra for patients and controls on the three testing occasions. First, we tested differences between controls and patients pre-ECT with an ANCOVA (described above). Controls outperformed patients tested before ECT on recall, $F(1,146)=4.56$, $p=0.034$, and on recognition, $F(1,143)=5.95$, $p=0.016$. Covariates affecting recall were gender, $F(1,146)=17{,}6$, $p<0.001$, education, $F(1,146)=15.1$, $p<0.001$, and age, $F(1,146)=5.46$, $p=0.021$, showing an advantage for men, better educated and older participants. Period also affected recall, $F(1,146)=25.47$, reflecting the effect of forgetting that increases with retention interval. This effect interacted with group, $F(1,146)=5.28$, $p=0.023$, as the score dropped more steeply with retention interval for controls than it did for patients. This might be caused by the effects of an increasing depression up to the moment of ECT. This may have led them to retain less of information about news events, which may have masked the effects of forgetting. For recognition, effects were seen of gender, $F(1,143)=6.81$, $p=0.01$, education, $F(1,143)=12.45$, $p=0.001$, and age, $F(1,143)=17.99$, showing an advantage of being male, better educated and older, compared to being female, less well educated, and younger. The effect of period was less strong than in recall, $F(1,143)=6.9$, $p=0.009$, reflecting generally less steep forgetting in recognition (Meeter et al., 2005); this did not interact with group, $F<1$.

To investigate whether ECT had caused retrograde amnesia immediately after treatment, we compared the pre-ECT and post-ECT scores at all periods, except the most recent 3 months (see above). Performance was significantly lower after ECT than before treatment, $F(1,16)=5.59$; $p=0.032$, suggesting that ECT had caused retrograde amnesia (effect size Cohen's $d=.36$). No effect was found for period, $F<1$. The interaction between period and testing occasions was not significant, $F<1$, suggesting that there was no strong gradient in retrograde amnesia. When the analysis was repeated with recognition scores, it yielded similar results with lower scores for the post- than the pre-ECT occasion, $F(1,16)=6.80$, $p=0.019$ (effect size Cohen's $d=.61$), no effect of period, $F<1$, and no interaction between occasion and period, $F(2,32)=1.71$, $p=0.196$. This suggests that immediately post-ECT, retrograde amnesia is found using recall and recognition measures and that it is ungraded, at least for the one-year period tested here.

We then investigated whether retrograde amnesia was still demonstrable 3 months after treatment had ended. For this, we compared periods three and four of the DNMT-ra pre-ECT and at follow-up. Pre-ECT and 3-month follow-up scores did not differ, $F(1,16)=1.69$, $p=0.21$. There was a trend towards an effect of period, $F(1,16)=3.4$, $p=0.09$, and no interaction between these two, $F<1$. For recognition, there was no effect of testing moment (pre-ECT vs. follow-up), of period and no interaction between these two, all $F<1$, when analyzed with covariates. This suggests that the retrograde amnesia seen immediately after ECT was no longer evident at 3-months follow-up, resulting in an improvement in scores that returned to the pre-ECT level (Fig. 1). However, Fig. 1 suggests that scores at pre-ECT and at follow-up were not the same, and this is also what an analysis without covariates suggested: in that analysis, a trend towards a lower follow-up than pre-ECT score was found, $F(1,20)=4.07$, $p=.057$. Confidence intervals (CI) around the mean difference between pre-ECT and follow-up were computed (95% CIs were [−.049, .123] for recall and [−.002, .125] for recognition); these suggested that only

Table 2
Characteristics of the patient sample and the matched control group.

	Patients (n = 21)		Controls (n = 131)	
Female	71%		72%	
	Mean	SD	Mean	SD
Age (years)	51.8	8.5	48.1	13.9
Education	3	1.86	3	1.43
Newspaper	2.6	2.73	2.9	2.41

Education refers to the highest attained level of education as measured on the seven-point scale standard in The Netherlands. Newspaper refers to the estimated number of newspapers read in one week, and is a measure of media exposure. Data are means and standard deviations (SD).

Table 3
Scores of patients on the Hamilton Depression Rating Scale (HDRS) and the ten-word test (10-WT) for anterograde memory function on the pre-ECT, post-ECT and follow-up test occasions.

	Pre-ECT		Post-ECT		Follow-up	
	Mean	SD	Mean	SD	Mean	SD
HDRS	25.6	4.4	9.3	6.9	11.2	8.3
10-WT	15.2	1.1	13.2	1.2	16.6	1.2

Data are means and standard deviations (SD).

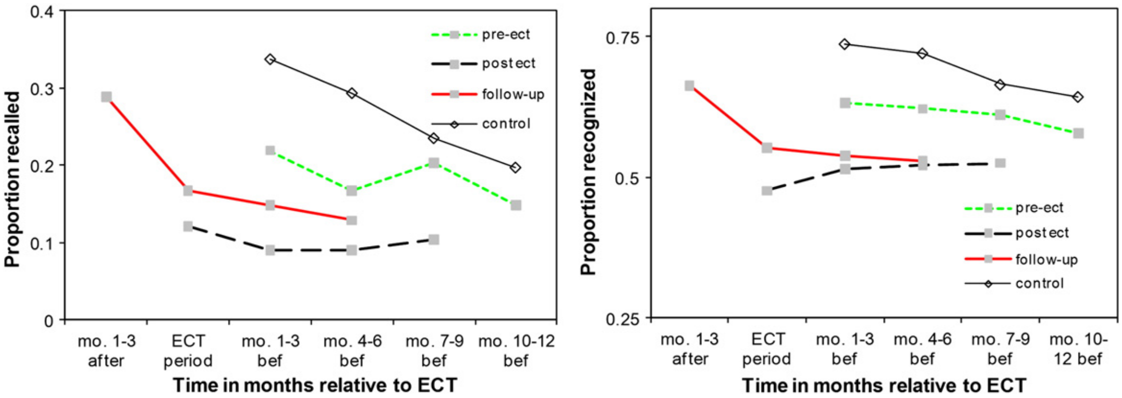

Fig. 1. Mean proportion of questions answered correctly on the DNMT-ra test of remote memory. This test contains questions on news events from four 3-month periods in the past: from the most recent 3 months to the period 10–12 months earlier. The two upper panels show results relative to the time of testing (left: recall and right: recognition), the two lower panels show results lined up relative to the period in which ECT was administered. The results are shown for patients tested on the day before ECT therapy started (pre-ect), within 3 days after ECT had ended (post-ect), and at 3-month follow-up. The upper panels also show results for the matched controls (ctrl).

moderate to large effects, d>.65, were definitely excluded by our data.

We then looked at memory of patients for news in the 3 months after ECT (period 1 at follow-up) with that of controls for the same period. No difference was found for recall, $t(150)=0.80$, $p=0.425$, or for recognition, $t(149)=1.51$, $p=0.133$, suggesting that after ECT patients were learning from the news at the same rate as normal controls.

3.4. Anterograde memory

For one patient, a technical failure ended the 10-WT of anterograde memory function on the pre-ECT testing occasion. In another patient, the staff considered it advisable to interrupt testing at the same pre-ECT occasion. For the 19 patients that did complete the test on all three test occasions, the following pattern was obtained: the average score decreased from pre-ECT to post-ECT and then increased at follow-up (Table 3). These changes were reliable when no covariates were included in the analysis, $F(2,36)=4.33$, $p=0.021$. With covariates, however, there was no effect of test occasion, and the only significant effect was an interaction between gender and test occasion, $F(2,26)=4.14$, $p=0.027$. Scores of male patients deteriorated from pre- to post-ECT and did not improve at follow-up (from 16.3 pre-ECT to 11.0 post-ECT and 12.3 at follow-up) whereas scores of female patients were not lower after ECT and did improve at follow-up (from 14.7 pre-ECT to 14.2 post-ECT, and to 18.5 at follow-up). Simple t-tests showed that only the difference between post-ECT scores and scores at follow-up was reliable, $t(20)=3.29$, $p=0.003$ (alpha corrected with Bonferroni correction for multiple tests).

To investigate the relation between anterograde and retrograde amnesia, we computed simple correlations between DNMT-ra and 10-WT scores at the three test occasions. We report correlations for the recognition scores on the DNMT-ra (correlations for recall scores were similar, but slightly lower). Anterograde memory pre-ECT, as indexed by 10-WT scores, correlated with DNMT-ra scores on all occasions ($r=0.56$ with pre-ECT scores, $r=0.60$ with post-ECT scores, and $r=0.64$ with follow-up scores, all significant at $p<0.025$). The 10-WT scores post-ECT correlated reliably only with post-ECT DNMT-ra scores ($r=0.44$, $p<0.05$ for post-ECT; $r=0.18$ for pre-ECT, $r=0.26$ for post-ECT, both NS). At follow-up, 10-WT scores did not correlate significantly with DNMT-ra scores at any occasion. The 10-WT scores pre- and post-ECT correlated with one another ($r=0.56$, $p<0.025$), as did the post-ECT and follow-up 10-WT scores ($r=0.50$, $p<0.025$). The correlation between pre-ECT and follow-up 10-WT scores did not reach significance ($r=0.40$). The DNMT-ra scores on all three occasions correlated with one another for all sets of measurements ($r>0.62$; $p<0.01$).

Neither DNMT-ra nor 10-WT scores correlated with the HDRS scores at any moment, nor with the related improvements or deteriorations.

Table 4
Means and standard deviations of the scores on the DNMT-ra for patients and controls.

	Month 1–3		Month 4–6		Month 7–9		Month10–12	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Recall								
Pre-ect	0.22	0.20	0.17	0.20	0.20	0.23	0.15	0.19
Post ect	0.12	0.20	0.09	0.13	0.09	0.15	0.10	0.16
Follow-up	0.29	0.23	0.17	0.13	0.15	0.18	0.13	0.11
Matched ctrl	0.34	0.27	0.29	0.26	0.23	0.20	0.20	0.21
Recognition								
Pre-ect	0.63	0.28	0.62	0.29	0.61	0.26	0.58	0.24
Post ect	0.48	0.20	0.51	0.24	0.52	0.26	0.53	0.22
Follow-up	0.66	0.21	0.55	0.20	0.54	0.26	0.53	0.21
Matched ctrl	0.74	0.21	0.72	0.21	0.67	0.20	0.64	0.23

4. Discussion

ECT has a reputation for causing retrograde amnesia. The present study suggests that such amnesia is indeed found immediately after ECT, but that it may mostly lift during the recovery period, as no retrograde amnesia was evident at 3-months follow-up. This was the case even though every patient was treated with bilateral ECT, which in previous studies was found to cause strong memory impairment

(Sackeim et al., 1993, 2000, 2009). Post-ECT retrograde amnesia may thus mainly be due to a temporary inability to access memories and not to ECT permanently erasing memories. However, our results come with the major caveat that the sample size was not large enough to exclude that a small to medium effect was undetected because of low power.

Our results do mirror earlier findings from anterograde amnesia, which is also usually restricted to the immediate post-ECT period (Sackeim et al., 1993; Brodaty et al., 2001). In the present study, anterograde memory showed no significant deterioration after ECT and had improved at follow-up. Performance on the retrograde and anterograde memory tests was correlated, reinforcing the interpretation of a period of confusion immediately after ECT, which then lifts to reveal either stable or even improved memory function at follow-up. Indeed, at follow-up patients performed at the same level as matched controls regarding retention of news events for the period after ECT.

Our way of analyzing the data eliminated the risk of confusing ECT's effect on remote memory (retrograde amnesia) with ECT's learning (anterograde amnesia). However, it introduced another risk of contamination. To assess the lasting impact of ECT on memory, we compared the two most remote periods of the DNMT-ra pre-ECT with the two most remote periods at follow-up. Since at follow-up these two periods coincided with the six months right before the ECT, depression was probably more severe for the periods included at the follow-up test occasion than at the pre-ECT test occasion (this can be appreciated in Fig. 1, the X-axis shows time relative to ECT; the two most remote data points for the follow-up line lie right before the ECT). This bias would be problematic if we had found lasting effects of ECT (since these could then be explained as the effect of increasingly severe depression instead). However, no such effects were found.

No gradient was found in the retrograde amnesia. This is not consistent with earlier reports, which found that ECT mostly affects recent memories (Squire et al., 1976; Cohen and Squire, 1981). This may be because in the present study only the year preceding ECT was tested, whereas in earlier reports memory was tested for much longer periods. Another reason for the inconsistency might be that, in the present study, a remote memory test was used that was well controlled, with items (selected on the basis of control data) known to be equivalent in difficulty. This precludes interpretation in terms of imbalances between test periods, a factor that may have hampered some previous studies. Recall performance was very low after ECT, which suggests that floor effects might have been another reason for a lack of gradient. However, floor effects did not occur on the recognition variant, in which no gradient was found either.

Before ECT, our patients performed worse on the test for retrograde amnesia than the controls. Moreover, this deficit correlated highly with pre-ECT anterograde memory function, suggesting a common underlying factor. A prime candidate for such a factor would be depression. Depression is known to be accompanied by moderate to severe memory deficits in most patients (Johnson and Magaro, 1987; Schaub et al., 2003). The lifting of depression could be the main ground for improvements seen in memory function at follow-up. Although neither retrograde nor anterograde memory function correlated with depression as measured by the HDRS, this lack of correlation could result from a restriction of range, since all participants suffered from severe mood disorder at pre-ECT testing (Sackeim et al., 2007, also found no correlation between the level of depression pre-ECT and retrograde amnesia, with a much larger sample than ours).

The pre-ECT impairments seen in patients suggest an alternative explanation for our findings. It could be that remote memory was impaired pre-ECT by depression, and that this impairment was lifted by the improvements in mood seen at follow-up. The fact that, at follow-up scores for pre-ECT periods were not better than they were before ECT, would then suggest that an ECT-induced impairment had replaced a depression-induced impairment in remote memory. Crucially, this interpretation rests on that memory deficits in depression are at least partly due to a recall deficit, as opposed to a learning deficit. If that were not the case, there would be no benefit for remote memories of the lifting of depression, and thus no space for an ECT-induced impairment to replace of a depression-induced impairment. Consistent with this interpretation, there was a trend towards some impairment at follow-up in recognition. In other words, it is possible that before ECT, patients could not recall news events due to depression. After ECT, recall of some memories was improved, but other memories were impacted by ECT and could thus not be recalled or recognized. Our data cannot refute this possibility, and since very few studies in the past have used recognition tests of remote memory, it remains difficult to assess.

Our results differ from those of O'Connor et al., who found severe retrograde amnesia at post-ECT follow-up for material studied before ECT (O'Connor et al., 2008); this follow-up was performed when disorientation had lifted according to a criterion test, which was on average 5 days after treatment had ended. Our follow-up period was 3 months; this difference in length of follow-up might (in part) explain the discrepancy between their results and ours. Moreover, O'Connor et al. (2008) relied on material studied just one or two days[1] before the start of the ECT course. Perhaps ECT causes pre-ictal amnesia for material learned immediately before treatment, but no broader retrograde amnesia. This would be consistent with reports on concussions, in which retrograde amnesia for short periods preceding the event are common (Kapur, 1999), and with findings from animal models of ECT, in which retrograde amnesia is typically found only for memories that were recently formed or had recently been activated (Lewis, 1979).

Another study with results contradicting our own is that of Sackeim et al. (2007). These authors followed a sample of 260 patients that were referred for ECT to one of several New York clinics. Patients were tested before and after ECT, and at a six-month follow-up. At follow-up patients obtained mostly higher scores on tests of cognitive abilities, with as two exceptions complex reaction time and, after bilateral electrode placement, remote autobiographical memory (right unilateral electrode placement did not lead to impairment of remote memory). The test used by these authors was the Columbia University Autobiographical Memory Interview-Short Form. In this test, participants generate memories to cues, which have to be remembered at later instances. This means that the score on the test is by necessity lower on later measurements than on the first. It also means that a low score does not necessarily reflect

[1] Margeret O'Connor, personal communication.

worse memory, but only that the set of memories generated during the baseline measurement could not be recalled. Therefore, a change in mental state from one measurement to the next (e.g., the lifting of depression) may result in lower scores due to well-known mood congruency effects in autobiographical recall (Bower, 1981). These considerations could explain why Sackeim et al. (2007) found lasting retrograde amnesia whereas we did not. Other explanations are also possible. It could be that autobiographical memory is more sensitive to ECT than memory for public events, or that that there are, in fact, lasting effects of ECT on remote memory that failed to reach significance in our study.

As mentioned above, our study lacked power to exclude small to medium lasting effects of ECT on remote memory. However, our results are also consistent with the possibility that modern ECT does not cause lasting retrograde amnesia. If so, what is the reason for earlier reports of retrograde amnesia? As reviewed by O'Connor et al. (2008), many of the studies compared memory before ECT with memory immediately after ECT, when disorientation may have caused inability to retrieve memories that were otherwise still accessible. Indeed, we found retrograde amnesia at our post-ECT test occasion, which for most patients was 1–2 days after their last ECT session. Moreover, earlier studies of ECT did not use dose titration and brief pulse stimulus as we did in this research. These technical improvements could have influenced our outcome compared to earlier research.

In the present study, the main limitation is lack of statistical power due to relatively small group sizes. This leaves open the possibility that our main null finding, i.e. no retrograde amnesia at follow-up, is in fact a type 2 error, although our results are inconsistent with large effects of ECT on remote memory.

In conclusion, our results leave open the possibility that ECT as currently practiced does not cause extensive lasting retrograde amnesia, and that the amnesia it does cause is mostly temporary.

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Conflict of interest

Dr. Murre and Dr. Janssen report no financial relationships with commercial interests. Dr. Meeter will in 2011 receive a consultancy fee for unrelated computational modeling work from Roche. Dr. Birkenhager has received study support from Lundbeck, and a speaker's honorarium from Servier, AstraZeneca and Wyeth. Dr. van den Broek has presented or organized scientific meetings for Wyeth and Servier.

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